PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Estimates of the 2016 Global Burden of Kidney Disease Attributable to Ambient Fine Particulate Matter Air Pollution
AUTHORS	Al-Aly, Ziyad; Bowe, Benjamin; Xie, Yan; Li, Tingting; Yan, Yan; Xian, Hong

VERSION 1 - REVIEW

REVIEWER	Goran Krstic Fraser Health, Canada
REVIEW RETURNED	14-Mar-2018

GENERAL COMMENTS	This is an observational epidemiological study of the Global Burden of Disease (GBD) focusing on the association between chronic kidney disease (CKD) and exposure to fine particulate matter air pollution (PM2.5). Despite an acknowledgement in the strengths and limitation of this study that “global burden of disease estimates while considered robust and reliable, are necessarily limited by the quality of the available data”, the authors conclude that their “results demonstrate that the global toll of CKD attributable to air pollution is significant” and that “air pollution may need to be considered in the discussion of the global epidemiology of CKD”. Although the conclusions appear to be supported by the presented statistical analyses, the authors indicate in the Methods section that “The GBD PM2.5 values are derived from the integration of satellite data, surface measurements, geographic data, and a chemical transport model, at an 11 by 11 km resolution, and then aggregated to national level population weighted means to produce a national exposure estimate”. Hence, a comprehensive discussion should be included in the current manuscript describing the ability of the applied satellite data at an 11 by 11 km resolution to predict accurately the concentrations of PM2.5 at the receptor level. Estimates of population exposure on the basis of air quality modeling, satellite data and/or land-use regression are associated with known limitations and uncertainties, which should be acknowledged for the reader. Available evidence from the published literature indicates that the correlation of land-use regression data vs. ground-level air pollution concentrations may not be sufficiently strong to allow reliable prediction/inferences for the population exposure. Land-use regression may be a convenient surrogate for site-/region-specific data. However, funnel-shaped (non-constant) scatter in regression plots can be observed in land-use regression models specifically for NO2 (r^2 of ~0.54 to 0.59) and PM2.5 (r^2 of ~0.42

	to 0.86) (see Wang et al., 2014 in Environ Health Perspect 122:843–849; http://dx.doi.org/10.1289/ehp.1307271). Hence, the use of modelled, satellite and/or land-use regression data as surrogates rather than actual measured ground-level air pollution data may introduce bias and could be considered as a major shortcoming of this study. Ideally, rather than a very coarse spatial resolution of 11 km2, one would require personal monitors to establish accurately population exposure to air pollution in urban environments. Ito et al., 2007 (Journal of Exposure Science and Environmental Epidemiology 17:S45–S60; doi:10.1038/sj.jes.7500627) indicate that “The air pollution variables showed a varying extent of intercorrelations with each other and with weather variables, and these correlations also varied across seasons. For example, NO2 exhibited the strongest negative correlation with wind speed among the pollutants considered, while ozone’s correlation with PM2.5 changed signs across the seasons (positive in summer and negative in winter). The extent of multi-collinearity problems also varied across pollutants and choice of health effects models commonly used in the literature. These results indicate that the health effects regression need to be run by season for some pollutants to provide the most meaningful results. We also find that model choice and interpretation needs to take into consideration the varying pollutant concurvities with the model co-variables in each pollutant’s health effects model specification”. Hence, it appears that the correlation and/or multi-collinearity issues between different air pollutants may also play a role in the suspected association between PM2.5 exposure and the global burden of chronic kidney disease in the current study. In addition, the authors should discuss for the reader in greater detail all study limitations, shortcomings and uncertainties. It is not clear if the authors have applied adequate control/adjustments for all reasonably foreseeable environmental, biological, behavioural and socio-economic confounding factors potentially associated with chronic kidney disease. For example, regional drinking water quality, food, diet and calcium supplementation appear not discussed at all in the submitted manuscript. Endemic nephropathy should be included in the assessment as well (see, for example, Gifford et al., 2017 paper on global epidemics of chronic kidney disease of unknown etiology (CKDu) and endemic nephropathy: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5362147/). Gifford et al., 2017 suggest that “The current body of evidence supports the theory of heat stress, arduous exercise, and inadequate hydration, in a genetically predisposed population or those exposed to a further insult such as agrochemicals”. It needs to be acknowledged for the reader that in the presence of confounding, an attribution fraction and causality would be difficult to determine for a weak health risk factor such as low levels of ambient air pollution. The authors should present a plausible mechanism of action of PM2.5 and its suspected role in the development of chronic kidney disease, with evidence from the published literature. CKD effects attributed specifically to low levels of PM2.5 exposure in urban environments should be discussed for the reader in greater detail (e.g., short- vs. long-term exposure, the shape of dose-response

	relationship, the presence/absence of a threshold exposure concentration, possible lag-time in response). Although the presented results may appear statistically significant, practical/clinical significance should be distinguished from a mere statistical significance. A large enough study population/sample is expected to yield statistically significant analytical results even if the actual difference between the study groups is so small that it could be considered essentially negligible and unimportant (e.g., not significant from a public health policy perspective). See some relevant published papers on statistical vs. practical (clinical) significance: Friedman, L. M. 2005. Clinical Significance versus Statistical Significance, Encyclopedia of Biostatistics, 2. http://onlinelibrary.wiley.com/doi/10.1002/0470011815.b2a01006/abstract ; Gelman and Stern, 2006: The Difference Between "Significant" and "Not Significant" is not Itself Statistically Significant. The American Statistician, Vol. 60, No. 4. http://www.stat.columbia.edu/~gelman/research/published/signif4.pdf ; and McCluskey and Lalkhen, 2007. Statistics IV: Interpreting the results of statistical tests. Contin Educ Anaesth Crit Care Pain, 7 (6): 208-212. http://ceaccp.oxfordjournals.org/content/7/6/208.full . The same concept can be used in large epidemiological studies on population health vs. regional differences in exposure to ambient air pollution. It should be observed that potentially unreliable small health risk estimates applied to very large populations may create a false impression of significant and measurable impacts in terms of attributable burden of disease, health care costs or life years saved. Young and Xia, 2013 (http://onlinelibrary.wiley.com/doi/10.1002/sam.11202/abstract) and Krstic, 2012 (http://www.tandfonline.com/doi/abs/10.1080/10962247.2012.697445) provide critical re-analyses of Pope et al. (2009) study on fine particulate matter air pollution (PM2.5) vs. life expectancy in the US (http://www.nejm.org/doi/pdf/10.1056/NEJMsa0805646). These papers illustrate the importance of adequate control for potentially significant confounding factors and the need to consider influential outliers, specific variable-attributable effects, and geographical heterogeneity. The authors should make the complete data-set from this study available to other researchers for re-analyses using different methodological approaches and for a test of consistency in the results and conclusions.

REVIEWER	Jennifer Bragg-Gresham, PhD, Assistant Research Scientist University of Michigan, USA
REVIEW RETURNED	06-Jul-2018

GENERAL COMMENTS	This is a very interesting application of the Bowe (2017) hazard ratios (HRs) correlating PM2.5 levels to CKD incidence. The authors have used standard PAF equations along with the HR's to estimate different measures of CKD burden in 194 countries.

	Major Comments: While I agree more attention needs to be paid to non-traditional risk factors for kidney disease, my main concern with this work is the causal implications inferred. The hazard ratios are based on observational data from the US Veteran's Affairs data, which although likely the best source for this data, is still observational and not representative of the US population. The authors appropriately accounted for patient-level confounders in that analysis, but missing from the discussion are other potential environmental factors. The worry here is that the authors are attributing the influence of multiple environmental factors solely to PM2.5. Have the authors examined any other factors such as water pollution or soil pesticide levels? This is particularly worrisome in regions with high CKD burden, likely due to other environmental causes, such as Central America/Sri Lanka, which are dealing with the epidemic of CKDu (CKD of unknown origin). Looking at estimates specific to these counties, PM2.5 levels are not exceptionally high, but estimates of burden being attributed to PM2.5 are very high when looked at as a rate per population size. I fear this could be misleading. Also, a reader naïve to this topic may not know the 2017 manuscript and may not got to the literature to understand the details. Since the HR's play such a prominent role in the current work, I feel the authors should include more description of the analyses that generated the HRs employed, while still referring the reader to the other manuscript for minute details. Another concern is that the HR's being used in all of these inferences are US-based, but being employed globally. Are there any estimates of the association between PM2.5 and CKD incidence outside the US that could be used as validation? I feel the authors should add a discussion of the above potential issues to the limitations and acknowledge that observational estimates are being employed to make causal inferences. Minor Comments: There were a few missing words in the text at the following locations: 1. Page 4, line 55: I believe the word "of" should go between network and collaborators. 2. Page 9, line 0 (first sentence): I think the word "for" should be between the words account and the.

REVIEWER	Dr Michael Waller School of Public Health University of Queensland
REVIEW RETURNED	27-Aug-2018

GENERAL COMMENTS	I have been asked to review this manuscript with a focus on the statistical methods used. I commend the authors on this detailed an interesting manuscript. The authors have carefully defined the study outcome and have frequently provided formulas for different measures used. Similarly the techniques used and reasons for different analysis decisions are well referenced throughout. In the results 'an interval of uncertainty' is presented with many outputs. This measure (based on percentiles) is a good alternative to confidence intervals which

	would be less meaningful in this analysis (due to very large denominators). The results presented in tables are very detailed (due to breakdowns by country), but of interest. In the main paper some novel visualisation techniques have been used to summarise the results. Perhaps in the Discussion the authors could reflect on which other confounding exposures (associated with both PM and CKD) not measured in their data-set they would have ideally liked to have adjusted for.

REVIEWER	Mieczyslaw Szyszkowicz Health Canada, Canada
REVIEW RETURNED	27-Aug-2018

GENERAL COMMENTS	As a reviewer I have the following remarks. 1. In strength and limitation: Please define CKD. 2. Page 4, Line 46: 11x11 km – I think it depends on geographical location (1 degree?). 3. Page 5, line 6: gender, please use sex –as latter (line 38) you are using “sex”. 4. Define BMI. 5. Define IQR. In both cases please spell these abbreviations. 6. Fix your references. Ref #7 is the same as Ref#22. 7. In many countries, say Guatemala, indoor exposure is very large (even open fire is used inside). Do you known/have any adjustments for such exposures? 8. Your study bases on log-linear models. Recent publications indicate more adequate approach: log-non-linear models. In such case the obtained estimates are different than traditional onel. Please see the publications: (a) “Global Estimates of Mortality Associated with Long Term Exposure to Outdoor Fine Particulate Matter” Burnett R. et al. PNAS, 2018. (b) Nasari M et al. A class of non-linear exposure-response models suitable for health impact assessment applicable to large cohort studies of ambient air pollution. Air Qual Atmos Health. 2016;9(8):961-972. Thank you

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

This is an observational epidemiological study of the Global Burden of Disease (GBD) focusing on the association between chronic kidney disease (CKD) and exposure to fine particulate matter air pollution (PM2.5). Despite an acknowledgement in the strengths and limitation of this study that “global burden of disease estimates while considered robust and reliable, are necessarily limited by the quality of the available data”, the authors conclude that their “results demonstrate that the global toll of CKD attributable to air pollution is significant” and that “air pollution may need to be considered in the discussion of the global epidemiology of CKD”.

Comment: Although the conclusions appear to be supported by the presented statistical analyses, the authors indicate in the Methods section that “The GBD PM2.5 values are derived from the integration of satellite data, surface measurements, geographic data, and a chemical transport model, at an 11 by 11 km resolution, and then aggregated to national level population weighted means to produce a national exposure estimate”. Hence, a comprehensive discussion should be included in the current manuscript describing the ability of the applied satellite data at an 11 by 11 km resolution to predict accurately the concentrations of PM2.5 at the receptor level. Estimates of population exposure on the basis of air quality modeling, satellite data and/or land-use regression are associated with known limitations and uncertainties, which should be acknowledged for the reader.

Available evidence from the published literature indicates that the correlation of land-use regression data vs. ground-level air pollution concentrations may not be sufficiently strong to allow reliable prediction/inferences for the population exposure. Land-use regression may be a convenient surrogate for site-/region-specific data. However, funnel-shaped (non-constant) scatter in regression plots can be observed in land-use regression models specifically for NO2 (r^2 of ~0.54 to 0.59) and PM2.5 (r^2 of ~0.42 to 0.86) (see Wang et al., 2014 in Environ Health Perspect 122:843–849; http://dx.doi.org/10.1289/ehp.1307271). Hence, the use of modelled, satellite and/or land-use regression data as surrogates rather than actual measured ground-level air pollution data may introduce bias and could be considered as a major shortcoming of this study. Ideally, rather than a very coarse spatial resolution of 11 km2, one would require personal monitors to establish accurately population exposure to air pollution in urban environments.

Response:

We thank the reviewer for this comment. We agree with the reviewer that national exposure estimates indeed have limitations and are not synonymous with individual level exposure. As the reviewer suggests, ideally personal monitors, or high resolution mobile sensors (for example Google air quality sensors mounted on Google Street View cars (http://apte.caee.utexas.edu/google-air-mapping/ and https://sustainability.google/projects/airview/) might provide more accurate estimates. We, however, note that this data is not yet available; furthermore, personal level measurements by personal monitors or ground-level measurements by air monitoring stations (or other platforms) for every populated area in the world is currently not available.

Comment: Ito et al., 2007 (Journal of Exposure Science and Environmental Epidemiology 17:S45–S60; doi:10.1038/sj.jes.7500627) indicate that “The air pollution variables showed a varying extent of intercorrelations with each other and with weather variables, and these correlations also varied across seasons. For example, NO2 exhibited the strongest negative correlation with wind speed among the pollutants considered, while ozone’s correlation with PM2.5 changed signs across the seasons (positive in summer and negative in winter). The extent of multi-collinearity problems also varied across pollutants and choice of health effects models commonly used in the literature. These results indicate that the health effects regression need to be run by season for some pollutants to provide the most meaningful results. We also find that model choice and interpretation needs to take into consideration the varying pollutant concurvities with the model co-variables in each pollutant’s health effects model specification”. Hence, it appears that the correlation and/or multi-collinearity issues between different air pollutants may also play a role in the suspected association between PM2.5 exposure and the global burden of chronic kidney disease in the current study. In addition, the authors should discuss for the reader in greater detail all study limitations, shortcomings and uncertainties.

Response:

We thank the reviewer for this comment. We have now included a discussion about limitations on seasonal effects and confounding by other pollutants/environmental factors.

Comment: It is not clear if the authors have applied adequate control/adjustments for all reasonably foreseeable environmental, biological, behavioural and socio-economic confounding factors potentially associated with chronic kidney disease. For example, regional drinking water quality, food, diet and calcium supplementation appear not discussed at all in the submitted manuscript. Endemic nephropathy should be included in the assessment as well (see, for example, Gifford et al., 2017 paper on global epidemics of chronic kidney disease of unknown etiology (CKDu) and endemic nephropathy: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5362147/). Gifford et al., 2017 suggest that “The current body of evidence supports the theory of heat stress, arduous exercise, and inadequate hydration, in a genetically predisposed population or those exposed to a further insult such as agrochemicals”.

Response:

We appreciate the reviewers comment. We have included additional details on prior work.

Beyond the adjustment factors listed in the manuscript, additional sensitivity analyses examined the within city effect to examine potential confounding by shared regional factors1, and controlled for 55 United States county-level variables in six domains, including demographics, physical environment, social and economic factors, health behaviors, clinical care, and health outcomes obtained from the U.S. County Health Ranking datasets2,3. The results were consistent with the estimated hazard ratio used in this study. However, it is true that their remains the possibility of residual confounding; this has been acknowledged in the limitations.

The GBD currently does not include CKD due to unknown origin as part of its casual framework, so this important issue could not be assessed. Here we focused on the overall burden of CKD irrespective of underlying cause; it is possible that the PAF differs by mix of etiology. We have acknowledged this limitation.

Comment: It needs to be acknowledged for the reader that in the presence of confounding, an attribution fraction and causality would be difficult to determine for a weak health risk factor such as low levels of ambient air pollution.

Response:

We appreciate the reviewers comment. We have now included further discussion on the analytic strategies developed in our prior work4 which were designed to address potential confounding, and have acknowledged limitations of the attributable fraction and casual interpretation.

Comment: The authors should present a plausible mechanism of action of PM2.5 and its suspected role in the development of chronic kidney disease, with evidence from the published literature. CKD effects attributed specifically to low levels of PM2.5 exposure in urban environments should be discussed for the reader in greater detail (e.g., short- vs. long-term exposure, the shape of dose-response relationship, the presence/absence of a threshold exposure concentration, possible lag-time in response).

Response:

Thank you for the comment. We now further elaborate on the putative mechanisms which may potentially explain the untoward effect of PM2.5 on the kidneys. “Three hypotheses have been proposed to explain the mechanisms by which PM2.5 may play a role in the development of CKD: Inhaled particular matter may result in pulmonary inflammation which could then lead to systematic inflammation. Pollutants may also induce disturbances in respiratory autonomic nervous system5.

Evidence has also suggested that particulate matter can enter the bloodstream and subsequently interacted with renal tissue."6

Comment: Although the presented results may appear statistically significant, practical/clinical significance should be distinguished from a mere statistical significance. A large enough study population/sample is expected to yield statistically significant analytical results even if the actual difference between the study groups is so small that it could be considered essentially negligible and unimportant (e.g., not significant from a public health policy perspective). See some relevant published papers on statistical vs. practical (clinical) significance:

Friedman, L. M. 2005. Clinical Significance versus Statistical Significance, Encyclopedia of Biostatistics, 2. http://onlinelibrary.wiley.com/doi/10.1002/0470011815.b2a01006/abstract ; Gelman and Stern, 2006: The Difference Between "Significant" and "Not Significant" is not Itself Statistically Significant. The American Statistician, Vol. 60, No. 4. http://www.stat.columbia.edu/~gelman/research/published/signif4.pdf ; and McCluskey and Lalkhen, 2007. Statistics IV: Interpreting the results of statistical tests. Contin Educ Anaesth Crit Care Pain, 7 (6): 208-212. http://ceaccp.oxfordjournals.org/content/7/6/208.full .

The same concept can be used in large epidemiological studies on population health vs. regional differences in exposure to ambient air pollution. It should be observed that potentially unreliable small health risk estimates applied to very large populations may create a false impression of significant and measurable impacts in terms of attributable burden of disease, health care costs or life years saved.

Response:

We thank the reviewer for the comment. We agree with the reviewer that statistical significance should not be equivocated to clinical or public health significance. To enhance the internal validity of the relationship and increase the possibility that the detected association was the true association between PM2.5 and CKD in the population we sampled from, in the previous paper we adjusted for individual and contextual risk factors that may confound the result. In addition, we applied various sensitivity analyses and applied ambient air sodium concentration as negative outcome control. The results were consistent across all analyses.

We have added to the discussion that as these estimates were applied to the Global CKD population, even marginal differences in the estimate would have profound impact on the attributable burden.

Comment: Young and Xia, 2013 (http://onlinelibrary.wiley.com/doi/10.1002/sam.11202/abstract) and Krstic, 2012 (http://www.tandfonline.com/doi/abs/10.1080/10962247.2012.697445) provide critical re-analyses of Pope et al. (2009) study on fine particulate matter air pollution (PM2.5) vs. life expectancy in the US (http://www.nejm.org/doi/pdf/10.1056/NEJMsa0805646). These papers illustrate the importance of adequate control for potentially significant confounding factors and the need to consider influential outliers, specific variable-attributable effects, and geographical heterogeneity.

Response:

We thank the reviewer for the comment. We have now added to the limitations of the risk estimations we used to generate the attributable burden, and have cited relevant literature.

Comment: The authors should make the complete data-set from this study available to other researchers for re-analyses using different methodological approaches and for a test of consistency in the results and conclusions.

Response:

Thank you for the comment. All data used in this study are publicly available, and sources are now correspondingly cited in the manuscript.

Reviewer: 2

This is a very interesting application of the Bowe (2017) hazard ratios (HRs) correlating PM2.5 levels to CKD incidence. The authors have used standard PAF equations along with the HR's to estimate different measures of CKD burden in 194 countries.

Major Comments:

Comment: While I agree more attention needs to be paid to non-traditional risk factors for kidney disease, my main concern with this work is the causal implications inferred. The hazard ratios are based on observational data from the US Veteran's Affairs data, which although likely the best source for this data, is still observational and not representative of the US population. The authors appropriately accounted for patient-level confounders in that analysis, but missing from the discussion are other potential environmental factors. The worry here is that the authors are attributing the influence of multiple environmental factors solely to PM2.5. Have the authors examined any other factors such as water pollution or soil pesticide levels?

Response:

We thank the reviewer for this comment. In our previous study, in addition to controlling for individual level characteristics, we a) built city-adjusted and within-city models to control for potential regional confounders, and b) additionally controlled for contextual factors including demographics, physical environment, social and economic factors, health behaviors, clinical care, and health outcomes which address confounding due to shared regional factors. Results from a negative control (air sodium concentrations) showed no association with CKD outcomes.

The reviewer is correct in that although we did take care to minimize confounding, it remains a possibility, and we have now added this to the limitation section.

Comment: This is particularly worrisome in regions with high CKD burden, likely due to other environmental causes, such as Central America/Sri Lanka, which are dealing with the epidemic of CKDu (CKD of unknown origin). Looking at estimates specific to these counties, PM2.5 levels are not exceptionally high, but estimates of burden being attributed to PM2.5 are very high when looked at as a rate per population size. I fear this could be misleading.

Response:

We thank the reviewer for this comment. Our estimates of CKD attributable to PM2.5 at the global and national levels reflect the influence not only of PM2.5 levels across the globe, but also of demography and underlying CKD rates. The ABD is comprised of both the risk attributable to PM2.5, and the rates of CKD in the country. We have included this in the discussion as well.

CKD of unknown etiology is an important and emerging entity; its causal driver has not been yet established.

In our analyses, we estimated the burden of CKD attributable to air pollution and did not undertake analyses by cause of CKD. Based on current literature it is unclear if the relationship between PM2.5 and CKD is mediated by other diseases (for example diabetes) or has an independent pathway.

Comment: Also, a reader naïve to this topic may not know the 2017 manuscript and may not got to the literature to understand the details. Since the HR's play such a prominent role in the current work,

I feel the authors should include more description of the analyses that generated the HRs employed, while still referring the reader to the other manuscript for minute details.

Response: We thank the reviewer for this comment. We have included a more thorough description of the work from which the HR was obtained.

Comment: Another concern is that the HR's being used in all of these inferences are US-based, but being employed globally. Are there any estimates of the association between PM2.5 and CKD incidence outside the US that could be used as validation?

Response: We thank the reviewer for this comment. The reviewer has pointed out a very important point. Currently the literature on ambient air pollution is limited; there are few studies in the US including a study by Mehta et al., also performed in veterans, and a study by Dr. Bragg-Gresham using a Medicare sample; these important studies were consistent in that they found an association between PM2.5 levels and kidney disease (reduction in eGFR levels and increased prevalence, respectively)7,8. Outside the US although there are a few studies from China that have suggested an association between PM2.5 and CKD, at the time of submission there had been no other estimates of PM2.5 and CKD incidence that could have been incorporated into this study. Very recently there was a cohort study in a Taiwanese population that further supported an association between PM2.5 and risk of CKD9. We now cite these recent publications in the manuscript.

As the HR was developed in a US cohort, despite robustness of the association to adjustment for multiple personal and environmental risk factors, we opted to plateau the risk at ranges outside those in US to reduce the level of extrapolation we were making. We have expanded upon discussion of the limits of generalizability.

Comment: I feel the authors should add a discussion of the above potential issues to the limitations and acknowledge that observational estimates are being employed to make causal inferences.

Response:

Thank you for this comment. We have included further discussion on limitations and noted that estimates from an observational study were used to estimate burden of disease.

Minor Comments:

There were a few missing words in the text at the following locations:

Comment: Page 4, line 55: I believe the word "of" should go between network and collaborators.

Response: Thank you. "of" has been added.

Comment: Page 9, line 0 (first sentence): I think the word "for" should be between the words account and the.

Response: Thank you. "for" has been added

Reviewer: 3

I have been asked to review this manuscript with a focus on the statistical methods used. I commend the authors on this detailed an interesting manuscript.

Comment: The authors have carefully defined the study outcome and have frequently provided formulas for different measures used. Similarly, the techniques used and reasons for different analysis decisions are well referenced throughout. In the results 'an interval of uncertainty' is

presented with many outputs. This measure (based on percentiles) is a good alternative to confidence intervals which would be less meaningful in this analysis (due to very large denominators). The results presented in tables are very detailed (due to breakdowns by country), but of interest. In the main paper some novel visualisation techniques have been used to summarise the results.

Response: Thank you for your comments.

Comment: Perhaps in the Discussion the authors could reflect on which other confounding exposures (associated with both PM and CKD) not measured in their data-set they would have ideally liked to have adjusted for.

Response: Thank you for this comment. We have included discussion on potential confounders not included in the analyses.

Reviewer: 4

As a reviewer I have the following remarks.

Comment: In strength and limitation: Please define CKD.

Response: Thank you. We have now defined CKD in the strengths and limitations.

Comment: Page 4, Line 46: 11x11 km – I think it depends on geographical location (1 degree?).

Response: Thank you for this comment. This is true. We have clarified that the GBD estimates were by 1 degree, which at the equator is approximately 11x11 km.

Comment: Page 5, line 6: gender, please use sex –as latter (line 38) you are using "sex".

Response: Thank you for this comment. Gender has been replaced with sex.

Comment: Define BMI.

Response: Thank you. BMI has been defined.

Comment: Define IQR. In both cases please spell these abbreviations.

Response: Thank you. IQR has been defined and spelled out.

Comment: Fix your references. Ref #7 is the same as Ref#22.

Response: Thank you. The references have been fixed.

Comment: In many countries, say Guatemala, indoor exposure is very large (even open fire is used inside). Do you known/have any adjustments for such exposures?

Response: Thank you for the comment. We did not have any data on indoor exposure to pollution, and the literature on the association between indoor exposure and CKD is, to the best of our knowledge, near non-existent. The intent of this study was to focus on outdoor air-pollution; this has been clarified. We now discuss lack of indoor air pollution data as one of our limitation.

Comment: Your study bases on log-linear models. Recent publications indicate more adequate approach: log-non-linear models. In such case the obtained estimates are different than traditional onel. Please see the publications: (a) "Global Estimates of Mortality Associated with Long Term Exposure to Outdoor Fine Particulate Matter" Burnett R. et al. PNAS, 2018. (b) Nasari M et al. A

class of non-linear exposure-response models suitable for health impact assessment applicable to large cohort studies of ambient air pollution. Air Qual Atmos Health. 2016;9(8):961-972.

Response: Thank you for the comment. Considerations of functional form are very important as they would have a large impact on the estimated population attributable fraction. In models for the estimate used in this study a spline analysis was conducted to investigate deviation from a linear relation to the log hazard. In that analysis, in the range of PM2.5 covered in the data, we did not observe any such deviation. A conservative approach that did not extrapolate trends seen in the data to exposure levels outside the range in the data was used, where we assumed PM2.5 levels above the range in the U.S. would have at least the same risk of CKD at the highest level in the US, plateauing the risk at that level (22.1 µg/m3). Future work should revisit this question to provide updated estimates of the burden of CKD attributable to ambient air pollution when more estimates for PM2.5 and CKD are available across the PM2.5 exposure spectrum for integrative meta-regression methods, where log-non-linear models should be considered.

VERSION 2 – REVIEW

REVIEWER	Goran Krstic Fraser Health, BC, Canada
REVIEW RETURNED	07-Nov-2018

GENERAL COMMENTS	The authors have adequately responded to the reviewers comments and provided an improved manuscript.

REVIEWER	Jennifer Bragg-Gresham University of Michigan, USA
REVIEW RETURNED	20-Dec-2018

GENERAL COMMENTS	This is a nice piece of analysis summarizing the global burden of CKD attributable to PM 2.5. While many assumptions had to be made to create the estimates, the authors used the most up to date values available, and this paper will hopefully bring more awareness to the high burden of disease due to environmental factors, such as air pollution.